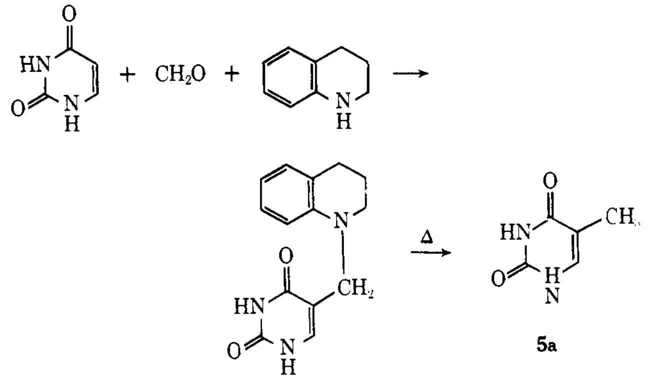
$NaBD_4$ to the alcohol, conversion to 5-chloromethyluracil-*methyl-d*, reaction with quinoline to give **3d** (mp 273–275°), and $NaBH_4$ reduction to **4d**. As in the example of **4c**, compound **4d** after heating to 205° gave thymine-*methyl-d* (**5c**, mass spectrum *m/e* (relative intensity) 128 (10), 127 (100), 126 (5)).

A crossover experiment wherein **4c** and **4d** were mixed and heated was run to establish an intramolecular process in the rearrangement. If the rearrangement went by an intramolecular process only thymine-*methyl-d* would be formed. An intermolecular process, assuming H and ^2H rearranged at the same rate, should lead to thymine, thymine-*methyl-d*, and thymine-*methyl-d*$_2$ in a ratio of 1:2:1. The mixed reaction of **4c** and **4d**, heated to 205° for 2 hr, gave thymine-*methyl-d* isolated in 6% yield (mass spectrum 70 eV *m/e* (relative intensity) 128 (27), 127 (100), 126 (38)).[6] Correcting for background it appears that the major portion of the product is derived from an intermolecular process. However, even in a neat melt of **4c** and **4d**, an intramolecular reaction does occur.

To complete the chemical model, a two-step reaction, alkylation and reduction, was performed. The first step, methylation, was accomplished by refluxing uracil, paraformaldehyde, and 1,2,3,4-tetrahydroquinoline for 72 hr in 75% ethanol to yield 1,2,3,4-tetrahydro-*N*-thyminylquinoline (**6**, 5%, mp 235–237°).



6

5a

Reduction to give thymine (**5a**, 10%) was done by heating **6** to 250° for 3 hr. Direct treatment of 5-hydroxymethyluracil with 1,2,3,4-tetrahydroquinoline failed to give thymine; a 3% yield of **6** was isolated.

Since the formation of thymine from uracil, formaldehyde, and a reducing agent, analogous to THFA, is chemically feasible through a bridged intermediate (**4a–d**), Friedkin's proposal employing structure **1** appears to be the most reasonable interpretation of the enzyme mechanism. An alternative mechanism, THFA reduction of the 5-hydroxymethyl derivative of dUMP, could not be confirmed in these models.

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[6] Authentic samples of thymine, thymine-*methyl-d*, and thymine-*methyl-d*$_2$ gave relative intensity backgrounds of the P + 1 *m/e* mass spectral peak of 10–18% of the P peak.

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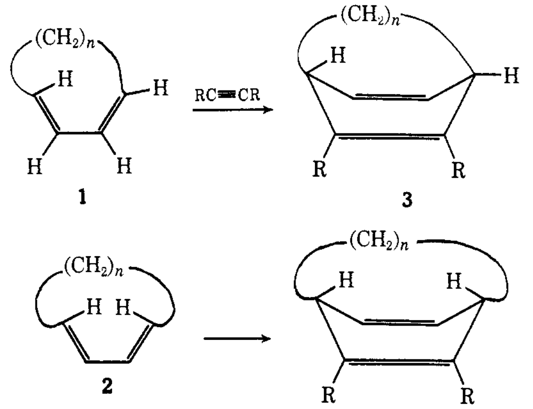
A Diels–Alder Approach to Inside–Outside Bicyclics[1]

Sir:

The synthesis and study of inside–outside (in–out) and inside–inside (in–in) bicyclics has been almost entirely limited to macrobicyclic systems having nitrogens at both bridgeheads.[2,3] In the form of their quaternary salts, these diazamacrobicyclics can exist in all three possible stereoisomeric forms. Since bridgehead stereochemistry has been achieved in these systems *via* reversible protonation, their method of synthesis is not readily extrapolated to the preparation of similar carbocyclic systems. We now wish to report that carbocyclic inside–outside bicyclics may be prepared through the addition of a suitable dienophile to a monocyclic *cis,trans*-1,3-diene.

In principle, concerted 2 + 4 Diels–Alder addition of dienophiles to cyclic conjugated *cis,trans*- and *trans,trans*-dienes, such as **1** and **2**, should yield inside–outside bicyclics (**3**) and inside–inside bicyclics (**4**), respectively. In practice, this approach is complicated by the tendency of certain small cyclic 1,3-dienes, which have at least one trans double bond, to undergo 2 + 2 addition of dienophiles[4] *via* the formation of diradical intermediates. In order to avoid this complication, we chose *cis,trans*-1,3-cyclododecadiene[5,6] (**5**), which has a relatively strain-free trans double bond, and perfluoro-2-butyne (**6**), which is a powerful dienophile but a poor participator in free-radical 2 + 2 additions,[7] as our reactants. When a 2.5:1 mixture of **6**:**5** was heated in a sealed tube at 150° for 42 hr, we obtained 78% of **7** and 16% of **8**, in addition to 2% of unreacted



1 **3**

2 **4**

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[1] Paper XXX on "The Chemistry of Bent Bonds." For the previous paper in this series, see P. G. Gassman and T. Nakai, *J. Amer. Chem. Soc.*, **94**, 5497 (1972).

[2] (a) H. E. Simmons and C. H. Park, *ibid.*, **90**, 2428, 2429, 2431 (1968); *Chem. Eng. News.*, 46 (July 3, 1967); C. H. Park and H. E. Simmons, U. S. Patent 3,531,468 (1970); *Chem. Abstr.*, **74**, 13189w (1971); (b) H. E. Simmons, C. H. Park, R. T. Uyeda, and M. F. Habibi, *Trans. N. Y. Acad. Sci.*, **32**, 521 (1970); (c) J. M. Lehn, J. P. Sauvage, and B. Dietrich, *J. Amer. Chem. Soc.*, **92**, 2916 (1970); *Tetrahedron Lett.*, 2885, 2889 (1969); (d) see also B. Metz, D. Moras, and R. Weiss, *Chem. Commun.*, 217 (1970).

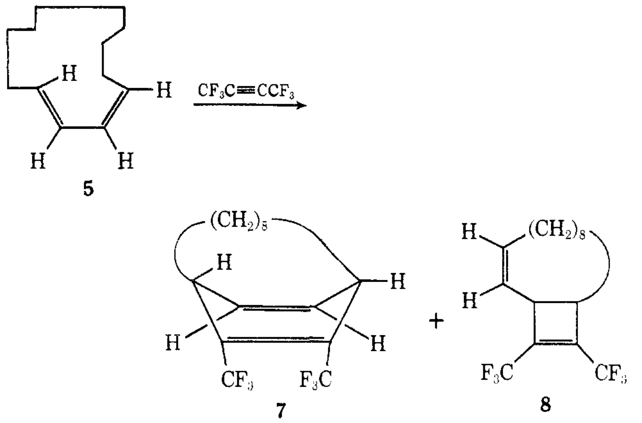
[3] For exceptions, see ref 2b.

[4] P. G. Gassman, H. P. Benecke, and T. J. Murphy, *Tetrahedron Lett.*, 1649 (1969).

[5] *cis,trans*-1,3-Cyclododecadiene was prepared from commercially available *trans*-cyclododecene by *N*-bromosuccinimide bromination, thermal dehydrobromination, and purification by chromatography on activity 1 basic alumina. This known[6] diene gave ir, nmr, and uv spectra consistent with the assigned structure.

[6] A. W. Fawcett and J. Harris, *J. Chem. Soc.*, 2673 (1954); British Patent 1,023,540 (1966); *Chem. Abstr.*, **64**, 19447g (1966).

[7] P. G. Gassman and K. T. Mansfield, *J. Amer. Chem. Soc.*, **90**, 1517 (1968).



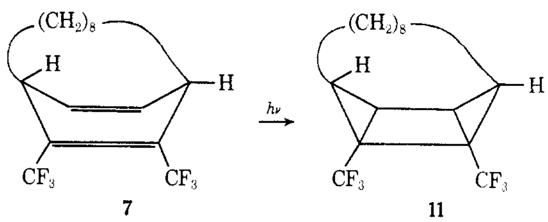
5. Both 7 and 8 were shown to be 1:1 adducts by mass spectrometry.[8]

The structure of 7 was established on the basis of both spectroscopic and chemical evidence. This major product showed no trans double bond absorption in the infrared, while exhibiting a strong cis double bond absorption at 14.05 μ.[9] Nmr spectroscopy showed two vinylic C–H resonances at τ 3.98 (d of d, J = 3.0 and 1.8 Hz) and 4.01 (br s). The bridgehead protons appeared as complex multiplets centered at τ 6.49 and 6.97. The peak at τ 6.97 is presumably due to the interior bridgehead proton which should feel the deshielding effects of the double bonds less than the external bridgehead proton. The remaining 16 protons appear as part of a complex pattern extending from τ 7.72 to 8.80.[9] The uv spectrum of 7 showed strong end absorption with a shoulder appearing at $\lambda_{\max}^{\text{isooctane}}$ 233 nm (ϵ 1370) consistent with a nonconjugated interaction between adjacent double bonds.[9]

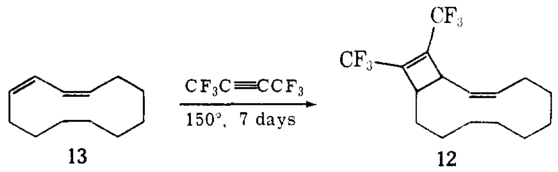
The mass spectral cracking pattern provided strong evidence for the proposed structure. The cleavage of the eight-membered bridge could be clearly detected and major peaks were observed corresponding to stepwise loss of each of the eight methylene units. The loss of the eight-carbon bridge gave *o*-ditrifluoromethylbenzene (**9**), *m/e* 214, as a major fragment. The subsequent fragmentation of this portion of the molecule corresponded to that of an authentic sample of **9** and to that observed below *m/e* 214 for 2,3-ditrifluoromethylbicyclo[2.2.2]octadiene (**10**).[10]

Finally, the proximity of the two double bonds could be demonstrated by the facile photochemical conversion of 7 into a saturated isomer (exact mass = 326.1466). In view of the well-established photochemical conversion of bicyclo[2.2.1]heptadiene into quadricyclane,[11] and of **10** into 1,6-ditrifluoromethyltetracyclo[4.2.0.^{2,8}0^{5,7}]octane,[10] this photoisomer of 7 has tentatively been assigned structure **11**. The mass spectral cracking pattern of **11** differed considerably from that of 7. In particular, the formation of **9** as a major fragmentation product was no longer observed.

The structural assignment for the minor product **8** was based on a combination of ir, uv, nmr, and mass spectral methods.



The ir spectrum showed only cis double bond absorption, while the uv spectrum showed no long-wavelength maximum similar to those observed for 7 and **10**.[10] The nmr spectrum of **8**, which was quite complex, also was consistent with the structure. The mass spectrum showed systematic loss of seven methylene units, but essentially no loss of the eighth methylene. This is consistent with the formation of a stable allylic species from **8**. More convincing evidence was obtained through comparison of the mass spectral cracking pattern of **8** with that of **12** (obtained as the only identifiable product from the reaction of **13** with perfluoro-2-butyne).[12] The cracking patterns of **8** and **12** were almost identical.



In summary, we have developed a simple, high-yield method for the synthesis of inside–outside bicyclics. The process outlined should be general, and should make these unusual bicyclic molecules readily available for further study. We are currently involved in a detailed study of the chemical properties of these molecules. In addition, we are investigating 2 + 4 cycloadditions to 1,3-*trans,trans*-cycloalkadienes as a route to inside–inside bicyclics.

Acknowledgment. We are indebted to the National Science Foundation for a grant which supported this investigation.

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(8) The exact mass of 7 was found to be 326.1466 (calcd *m/e* 326.1469), and that of 8 was 326.1474.

(9) 2,3-Ditrifluoromethylbicyclo[2.2.2]octadiene (10)[10] served as a useful model for spectral comparison purposes: ir 14.20 μ; nmr τ 3.56 (vinyl protons, d of d), 5.91 (bridgehead protons, br m); uv, shoulder at $\lambda_{\max}^{\text{acetonitrile}}$ 234 nm (ϵ 950).

(10) R. S. H. Liu, *Tetrahedron Lett.*, 1409 (1969).

(11) F. I. Sonntag and R. Srinivasan, *Org. Photochem. Syn.*, 1, 97 (1971), and references contained therein.

(12) Models indicate that the cisoid configuration of the butadiene moiety of 13 would require a significantly strained distortion of the whole molecule. Thus, 13 would not be expected to readily yield a Diels–Alder type product.

(13) The Ohio State University Postdoctoral Fellow, 1971–1972.

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Bicyclo[8.8.8]hexacosane. Out,In Isomerism

Sir:

Bridgehead protons in small bicyclic molecules, such as bicyclo[2.2.2]octane, occupy space exclusively outside the hydrocarbon cavity of the ring system. Relative to the three methylene chains, the bridgehead carbon atoms are of an opposite spatial sense. Isomers which have one or both of the bridgehead protons located inside of the cavity would be exceedingly unstable as a result of intolerable bond angle deformation and nonbonded interactions.[1] These structural restrictions are, however, relaxed as soon as the constituent rings

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(1) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, New York, N. Y., 1966, p 102.